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PAPER

Suzuki–Miyaura cross coupling reactions with Phenoldiazonium salts†

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The Suzuki–Miyaura coupling of phenol diazonium salts and aryl trifluoroborates yields 4-hydroxybiaryls in a protecting group-free synthesis.

Introduction

4-Hydroxybiaryls are structural motifs present in many drugs, drug candidates or compounds which are otherwise of interest in medicinal chemistry. A representative example is diflunisal (**1**), an antiinflammatory drug which acts by inhibition of cyclooxygenase-2 (Fig. 1).[1] Analogues of diflunisal were synthesized with the aim to study and eventually reduce its undesired binding to human serum albumin, which causes a significant loss of efficacy and makes rather high dosing of the drug necessary.[2] The discovery that several non-steroidal anti inflammatory drugs (NSAID's) stabilize the native structure of the amyloidogenic plasma protein transthyretin (TTR) sparked new interest in these drugs.[3] Thus, analogues of flufenamic acid,[4] diclofenac,[5] flurbiprofen[6,7] and diflunisal[8] were synthesized and evaluated for their potency as amyloidogenesis inhibitors. From the crystal structures of TTR-drug complexes[6] it was deduced that small molecule inhibitors should have two aromatic moieties and at least one polar functional group. Therefore, numerous biaryls were included in a screening for TTR amyloid fibril inhibitors and identified as promising lead structures.[9] 4-Hydroxybiaryls have also been used as intermediates in the synthesis of pharmacologically relevant compounds, such as the H_3 receptor antagonist **2**, which is available in few steps from phenol **3** (Fig. 1).[10]

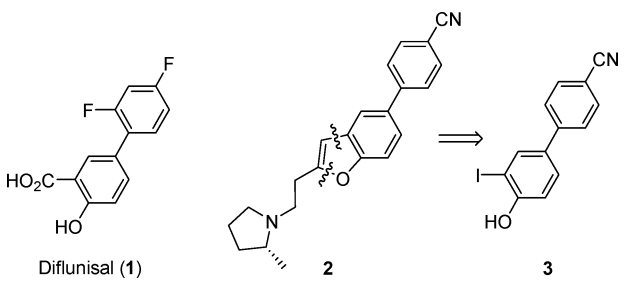

Fig. 1 Target molecules containing the 4-hydroxybiaryl motif.

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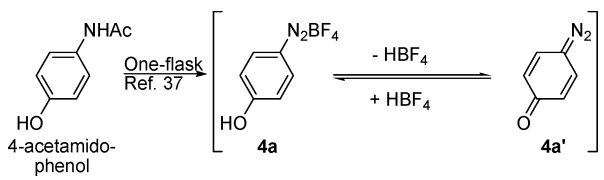
† Electronic supplementary information (ESI) available: Experimental details for all new compounds and copies of ^{1}H and ^{13}C-NMR spectra. See DOI: 10.1039/c1ob05256j

The most commonly used methods for the synthesis of biaryl compounds are Pd-catalyzed cross coupling reactions.[11,12] In particular, the Suzuki–Miyaura reaction[13] is a valuable tool for this purpose. In most cases, aryl halides are used as electrophiles in this transformation, with aryl iodides being significantly more reactive than aryl bromides or -chlorides. However, a major disadvantage of aromatic iodo compounds is their light sensitivity and the comparatively high price. Over the past two decades, arene diazonium salts were established as interesting alternatives in various Pd-catalyzed C–C-bond forming reactions,[14–16] including Suzuki–Miyaura cross coupling reactions with boronic acids,[17–23] boronates,[24] dioxazaborocanes[25] and organotrifluoroborates.[26–30] While unprotected iodophenols have been successfully used in Suzuki–Miyaura couplings,[31,32] free phenol diazonium salts have, to the best of our knowledge, never been investigated. A single example of a biaryl formation from a phenol diazonium compound was reported by Goeldner *et al.*, however, this reaction is a photochemical C–H-insertion and proceeds *via* a different mechanism.[33] We have very recently reported, that arene diazonium salts can be synthesized from acetanilides in a one-flask deacetylation-diazotation sequence.[34,35] This method can be extended to phenol diazonium salts, which were found to be superior arylating agents in Mizoroki–Heck-reactions than their O-alkylated analogues.[36,37] In the course of this study, we discovered that the preferred conditions for these Mizoroki–Heck-reactions are methanol as a solvent and addition of a base, whereas basefree conditions are advantageous if alkoxy arene diazonium salts are used.[37] As a working hypothesis, we proposed that phenol diazonium cations such as **4a** are protected against hydrodediazonation under the preferred conditions by partial or complete deprotonation. This results in the formation of a quinone diazide structure **4a′**, which is supported by NMR-spectroscopical investigations (Scheme 1).[37]



Scheme 1 Phenol diazonium *vs.* quinone diazide structure.

The interesting results obtained in Mizoroki–Heck reactions with phenol diazonium salts **4** and the attractive perspective of a

protecting group free synthesis of 4-hydroxy biaryls under mild conditions prompted us to investigate these reagents in Suzuki-Miyaura coupling reactions.

Results and discussion

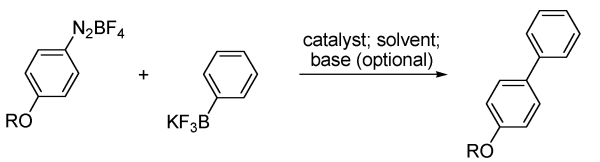
We started with a comparison of 4-phenol diazonium salt **4a** and its O-methyl derivative **4b**. As organotrifluoroborates[26] are readily available,[38] very stable and highly nucleophilic reagents for Suzuki–Miyaura coupling reactions,[30] we chose potassium phenyltrifluoroborate **5a** for the initial reactions. For practical purposes, $Pd(OAc)_2$ and Pd/C are the most convenient precatalysts, and we therefore decided to test both in this study. The Suzuki–Miyaura coupling of non-phenolic arene diazonium salts and organotrifluoroborates has previously been accomplished by Genêt *et al.*,[28] who identified $Pd(OAc)_2$ in dioxane in the absence of a base as best conditions. Based on the experiences we made during the investigation of Mizoroki–Heck reactions, we decided to test in addition to Genêt's conditions, methanol as a solvent and optional addition of NaOAc as a base (Table 1).

The results listed in Table 1 confirm that for 4-methoxy-benzene diazonium salt **4b** Genêt's conditions (entry 1) give the highest yields of coupling product **6ba**. In methanol, the isolated yield is significantly lower, but still useful (entry 2). The combination of methanol as a solvent and addition of a base, however, results in a low yield of 32% (entry 3). This observation is in accord with results obtained for the Mizoroki–Heck reaction of **4b** and methyl acrylate and can be attributed to a competing decomposition of the diazonium salt in the presence of nucleophiles.[37] No conversion to the desired coupling product was observed with Pd/C in dioxane (entry 4),[20] whereas a fair yield of **6ba** was obtained with this catalyst in methanol (entry 5). The same conditions were then applied to phenol diazonium salt **4a**. In contrast to **4b** and other non-phenolic diazonium salts, dioxane is not a suitable solvent in this case (entry 6). Switching to methanol results in a significantly improved yield of 70% (entry 7), which can be further improved to 82% by addition of a base (entry 8). Replacing $Pd(OAc)_2$ by Pd/C as a catalyst gives very similar results as for **4b** (entries 9 and 10). It should be noted that Pd/C can be a highly active catalyst for Suzuki–Miyaura coupling reactions with arene diazonium salts, however, parameters such as particle size, distribution of the metal and degree of reduction play a crucial role.[22] These parameters are difficult to control if the catalyst was obtained from a commercial source. As a result of the findings described above, we refrained from using Pd/C and dioxane in further experiments. However, we have previously observed that the beneficial effect of added base is not general for all phenol diazonium salts and therefore decided to test both basic and base-free conditions, using methanol as a solvent and $Pd(OAc)_2$ as a catalyst. The results of this investigation into the scope and limitations of Suzuki–Miyaura-couplings with unprotected phenol diazonium salts are summarized in Table 2.

The reaction of **4a** with substituted arene trifluoroborates **5b,c** gives results which are similar to those obtained with **5a**: addition of a base (entries 1 and 3 *vs.* entries 2 and 4) substantially improves the yield of coupling products **6ab** and **6ac**. Remarkably, the attempted cross coupling with amide-substituted trifluoroborate **5e** fails completely both under basic and base-free conditions, and we could neither isolate **6ae** nor any homocoupling products (entries 5 and 6). As expected from the results discussed above, cross coupling reactions of 4-methoxy substituted diazonium salt **4b** with **5b,c** are preferably conducted under base-free conditions (entries 7–10). The reaction of **4b** with **5c** (entry 9) is remarkable, as this is the only example where we observed a significant amount of an aryltrifluoroborate-homocoupling product. In this experiment, the desired cross coupling product **6bc** and a symmetrical biaryl were obtained as an inseparable mixture in a 5 : 1 ratio (Scheme 2).

Formation of such homocoupling products has been reported as a side reaction in Suzuki–Miyaura couplings with aryl boronic acids, when oxygen was not rigorously excluded.[39,40] Very recently, Lloyd-Jones *et al.* investigated the mechanism of Suzuki–Miyaura reactions with organotrifluoroborates in detail and proposed a rationale for the observation that homocoupling products are

Table 1 Optimization of conditions for the coupling of **4a,b** and **5a**[a]



4a (R = -H) **4b** (R = -CH_3) **5a** **6aa** (R = -H) **6ba** (R = -CH_3)

Entry	**4**	Catalyst	NaOAc (equiv.)	Solvent	Product	Yield
1	***4b***	*$Pd(OAc)_2$*	*none*	*dioxane*	***6ba***	*79%*
2	**4b**	$Pd(OAc)_2$	none	methanol	**6ba**	64%
3	**4b**	$Pd(OAc)_2$	3.0	methanol	**6ba**	32%
4	**4b**	Pd/C	none	dioxane	**6ba**	0%
5	**4b**	Pd/C	none	methanol	**6ba**	48%
6	**4a**	$Pd(OAc)_2$	none	dioxane	**6aa**	18%
7	**4a**	$Pd(OAc)_2$	none	methanol	**6aa**	70%
8	***4a***	*$Pd(OAc)_2$*	*3.0*	*methanol*	***6aa***	*82%*
9	**4a**	Pd/C	none	dioxane	**6aa**	0%
10	**4a**	Pd/C	none	methanol	**6aa**	41%

[a] Reagents and conditions: **4a** or **4b** (1.0 equiv.), **5a** (1.0 equiv.), solvent (10 mL $mmol^{-1}$), then add NaOAc (3.0 equiv., optional), then add catalyst (2.5 mol%), 20 °C, 12 h.

Table 2 Suzuki–Miyaura coupling reactions with various 4-phenol diazonium salts[a]

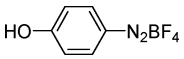
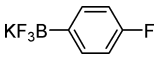
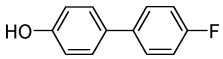
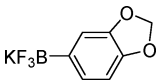
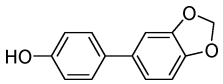
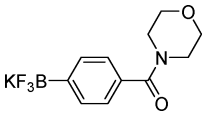
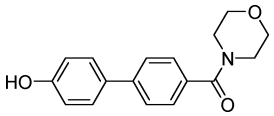
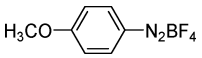
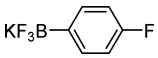
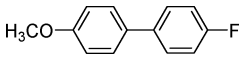
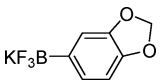
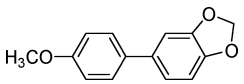
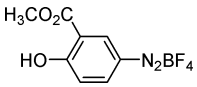
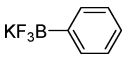
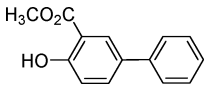
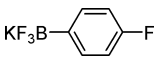
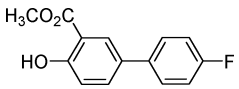
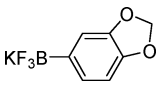
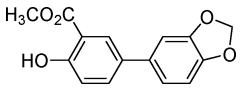
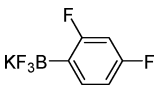
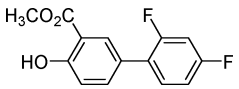
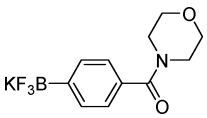
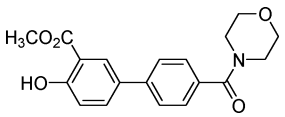
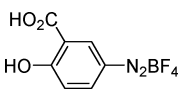
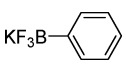
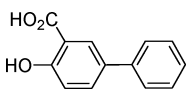
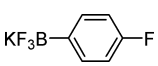
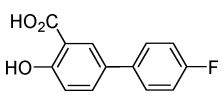
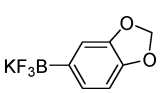
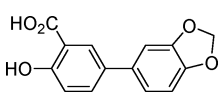
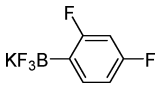
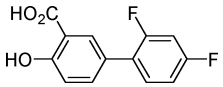
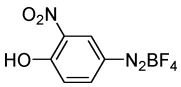
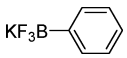
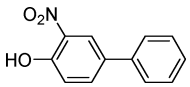
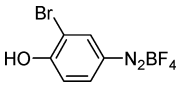
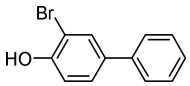
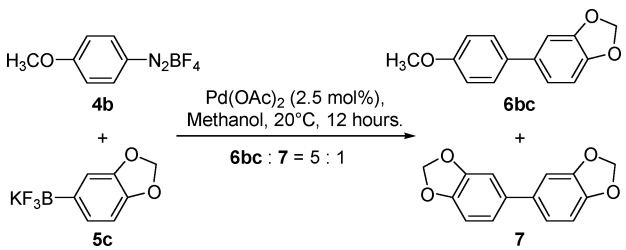
Entry	ArN_2BF_4	4	$Ar'BF_3K$	5	NaOAc (equiv.)	Ar–Ar′	6	Yield
1		**4a**		**5b**	none		**6ab**	36%
2					3.0			74%
3				**5c**	none		**6ac**	48%
4					3.0			66%
5				**5e**	none		**6ae**	< 5%
6					3.0			< 5%
7		**4b**		**5b**	none		**6bb**	40%
8					3.0			16%
9				**5c**	none		**6bc**	(94%)[b]
10					3.0			36%
11		**4c**		**5a**	none		**6ca**	70%
12					3.0			< 5%
13				**5b**	none		**6cb**	82%
14					3.0			< 5%
15				**5c**	none		**6cc**	44%
16					3.0			< 5%
17				**5d**	none		**6cd**	99%
18				**5e**	none		**6ce**	70%
19		**4d**		**5a**	none		**6da**	59%
20					3.0			18%
21				**5b**	none		**6db**	34%
22					3.0			27%
23				**5c**	none		**6dc**	46%
24					3.0			31%

Table 2 *(Contd.)*

Entry	ArN_2BF_4	4	$Ar'BF_3K$	5	NaOAc (equiv.)	Ar–Ar′	6	Yield
25				**5d**	none		**1**	34%
26		**4e**		**5a**	none		**6ea**	94%
27					3.0			56%
28		**4f**			none		**6fa**	44%
29					3.0			18%

[a] Reagents and conditions: **4** (1.0 equiv.), **5a** (1.0 equiv.), methanol (10 mL $mmol^{-1}$), NaOAc (3.0 equiv., optional), $Pd(OAc)_2$ (2.5 mol%), 20 °C, 12 h. [b] Yield is based on trifluoroborate **5c** and refers to an inseparable 5 : 1 mixture of **6bc** and homocoupling product 7.



Scheme 2 Suzuki–Miyaura coupling of **4b** and **5c** with competing formation of homocoupling product **7**.

formed in significantly smaller amounts with these reagents. For phosphine containing catalysts, fluoride ions can accelerate the reduction of the Pd(II)-precatalyst in the presence of water, thereby suppressing the oxidative homocoupling of boronates.[41] However, in the absence of phosphine ligands and water this explanation appears to be improbable. It is more likely that hydrolysis of the aryltrifluoroborates under our reaction conditions is slow,[42] and the suppressed formation of homocoupling products may be attributed to a low concentration of boronic acid. This would, as outlined by Lloyd-Jones *et al.*, imply that the transmetallation step in the catalytic cycle occurs directly from the aryl trifluoroborate.[41]

We do not know whether or not this explains our findings, but it is striking that the formation of a homocoupling product is an exception under the conditions used by us. In those cases where conversions and isolated yields are rather low, products resulting from a hydrodediazonation could be detected, but no homocoupling products.

Next, we extended our investigations to *meta*-substituted 4-phenol diazonium salts **4c–f** (entries 11 to 29). The most important result from these experiments is that in contrast to **4a** base-free conditions are strongly preferred. This observation might be explained by a reduced participation of a quinone diazide structure analogous to **4a′**, if electron withdrawing groups are located *ortho* to the phenol. Under these circumstances, the beneficial effect of added base (*i.e.* quinone diazide formation) is probably outweighed by the detrimental effect of nucleophiles on the stability of diazonium salts. Particularly useful for target molecule synthesis is diazonium salt **4c**. For example, diflunisal methylester (**6cd**, entry 17) was obtained quantitatively, and morpholino amide **6ce** (entry 18), a potential H_3-antagonist precursor, in 70% yield.[10] This result is remarkable, considering the complete failure for **6ae** (entries 5, 6). Suzuki–Miyaura coupling reactions with the highly polar carboxylic acid diazonium salt **4d** were also successful, *e.g.* for the synthesis of diflunisal (**1**, entry 25).

Conclusions

In summary, various 4-hydroxy biaryls are accessible in a protecting group free Suzuki-Miyaura coupling from phenol diazonium salts and aryl trifluoroborates. Depending on the diazonium salt used, basic or base-free conditions are preferred. The precatalyst $Pd(OAc)_2$ gives good yields and selectivities in most cases and makes sophisticated catalytic systems unnecessary for these reactions.

Experimental

General remarks

All experiments were conducted in dry reaction vessels under an atmosphere of dry nitrogen. Solvents were purified by standard procedures. ^{1}H NMR spectra were obtained at 300 MHz in $CDCl_3$ with $CHCl_3$ ($\delta = 7.26$ ppm) as an internal standard, or in methanol-d_4 with CD_2HOD ($\delta = 3.31$ ppm) as an internal standard. Coupling constants (J) are given in Hz. ^{13}C NMR spectra were recorded at 75 MHz in $CDCl_3$ with $CDCl_3$ (δ = 77.0 ppm) as an internal standard or in methanol-d_4 with CD_3OD (δ = 49.2 ppm) as an internal standard. The number of coupled protons was analyzed by DEPT- or APT-experiments and is denoted by a number in parantheses following the chemical shift value. Whenever signal assignments in ^{1}H- or ^{13}C-NMR spectra are given, these are based on H,H- and H,C-correlation spectroscopy, and NOE-spectroscopy if necessary. ^{19}F NMR spectra were recorded at 282 MHz in $CDCl_3$ with C_6F_6 (δ = –163 ppm) as an internal standard. IR spectra were recorded in substance on NaCl or KBr plates. Wavenumbers (ν) are given in cm^{-1}. The peak intensities are defined as strong (s), medium (m) or weak (w). Mass spectra were obtained at 70 eV.

General experimental procedures

Basic conditions. To a solution of the appropriate diazonium salt **4** (0.5 mmol) in methanol (5.0 mL) were added NaOAc (123 mg, 1.5 mmol) and $Pd(OAc)_2$ (2.8 mg, 2.5 mol%). The mixture was stirred at ambient temperature for 10 min, and the appropriate potassium trifluoroborate **5** (0.5 mmol) was added. Stirring at ambient temperature was continued for 12 h, and active charcoal (100 mg) was added. All volatiles were removed *in vacuo*, ethyl acetate (25 mL) or MTBE (100 mL) was added and the mixture was immersed in an ultrasonic bath. It was then filtered through celite, the solvent was evaporated and the residue was purified by chromatography on silica using the eluents stated for the individual examples.

Base-free conditions. To a solution of the appropriate diazonium salt **4** (0.5 mmol) in methanol (5.0 mL) was added $Pd(OAc)_2$ (2.8 mg, 2.5 mol%). The mixture was stirred for 10 min, and the appropriate potassium trifluoroborate **5** (0.5 mmol) was added. Stirring at ambient temperature was continued for 12 h, and active charcoal (100 mg) was added. All volatiles were removed *in vacuo*, ethyl acetate (25 mL) or MTBE (100 mL) was added and the mixture was immersed in an ultrasonic bath. It was then filtered through celite, the solvent was evaporated and the residue was purified by chromatography on silica using the eluents stated for the individual examples.

Analytical data and details

Biphenyl-4-ol (6aa). The title compound was obtained from **4a** (104 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using basic conditions as a colourless solid, mp 162–164 °C.[43] Yield: 70 mg, 82%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.55–7.50 (2H), 7.44 (d, J = 8.7, 2H), 7.40–7.33 (2H), 7.24 (m, 1H), 6.85 (d, J = 8.7, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 158.3 (0), 142.6 (0), 134.0 (0), 129.8 (1), 129.2 (1), 127.6 (1), 127.5 (1), 116.8 (1); IR (neat) ν 3421 (w), 1598 (w), 1534 (w), 1489 (w), 1263 (w); MS (ESI): m/z 170 ([M]$^+$, 10), 122 (100); HRMS (ESI): calcd. for $C_{12}H_{11}O[M+H]^+$: 171.0810, found: 171.0819; Anal. calcd. for $C_{12}H_{10}O$: C, 84.7; H, 5.9. Found: C, 84.2; H, 5.8.

4′-Fluorobiphenyl-4-ol (6ab). The title compound was obtained from **4a** (104 mg, 0.5 mmol) and **5b** (101 mg, 0.5 mmol) using basic conditions as a colourless solid, mp 167–170 °C.[44] Yield: 69 mg, 74%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.50 (dd, J = 8.2, 5.6, 2H), 7.39 (d, J = 8.5, 2H), 7.10 (d, J = 8.7, 1H), 7.06 (d, J = 8.7, 1H), 6.84 (d, J = 8.7, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 162.6 (d, J = 242.3, 0), 157.1 (0), 137.8 (d, J = 3.0, 0), 131.9 (0), 128.1 (d, J = 8.3, 1), 127.9 (1), 115.7 (1), 115.3 (d, J = 21.0, 1); ^{19}F NMR (282 MHz, MeOD-d_4) δ −117.2 (tt, J = 8.8, 5.3); IR (neat): ν 3406 (w), 1600 (w), 1500 (m), 1450 (w), 1375 (w), 1246 (m), 1164 (w); MS (ESI): m/z 188 ([M]$^+$, 100), 159 (27), 133 (22); HRMS (ESI): calcd. for $C_{12}H_{10}FO[M+H]^+$: 189.0716, found: 189.0734; Anal. calcd. for $C_{12}H_9FO$: C, 76.6; H, 4.8. Found: C, 76.4; H, 4.8.

4-(Benzo[d][1,3]dioxol-5-yl)phenol (6ac). The title compound was obtained from **4a** (104 mg, 0.5 mmol) and **5c** (114 mg, 0.5 mmol) using basic conditions as a colourless solid, mp 143–144 °C. Yield: 71 mg, 66%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.34 (d, J = 8.7, 2H), 7.03–6.94 (2H), 6.82 (m, 1H), 6.81 (d, J = 8.7, 2H), 5.93 (s, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 157.9 (0), 149.7 (0), 148.0 (0), 137.1 (0), 133.9 (0), 128.9 (1), 120.9 (1), 116.7 (1), 109.5 (1), 108.1 (1), 102.4 (2); IR (neat): ν 3420 (w), 2888 (w), 1610 (w), 1491 (m), 1239 (m), 1110 (w), 1044 (m); MS (ESI): m/z 214 ([M]$^+$, 28), 194 (100); HRMS (ESI): calcd. for $C_{13}H_{11}O_3[M+H]^+$: 215.0708, found: 215.0708.

4-Methoxybiphenyl (6ba). The title compound was obtained from **4b** (111 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 86–87 °C.[45] Yield: 58 mg, 64%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60–7.56 (2H), 7.56 (d, J = 8.8, 2H), 7.48–7.40 (2H), 7.36–7.29 (m, 1H), 7.01 (d, J = 8.8, 2H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.2 (0), 140.8 (0), 133.8 (0), 128.7 (1), 128.1 (1), 126.7 (1), 114.2 (1), 55.4 (3); IR (neat) ν 3003 (w), 1607 (m), 1487 (m), 1250 (s); Anal. calcd. for $C_{13}H_{12}O$: C, 84.8; H, 6.6. Found: C, 84.8; H, 6.3.

4-Fluoro-4′-methoxybiphenyl (6bb). The title compound was obtained from **4b** (111 mg, 0.5 mmol) and **5b** (101 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 88–91 °C.[46] Yield: 40 mg, 40%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50 (dd, J = 8.9, 5.2, 2H), 7.48 (d, J = 8.9, 2H), 7.11 (dd, J = 8.7, 8.7, 2H), 6.98 (d, J = 8.7, 2H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.1 (d, J = 245.6, 0), 159.1 (0), 132.8 (0), 137.0 (d, J = 3.2, 0), 128.2 (d, J = 7.9, 1), 128.0 (1), 115.5 (d, J = 21.4, 1), 114.2 (1), 55.3 (3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.9 (tt, J = 5.3, 3.3); IR (neat) ν 2920 (w), 1606 (w), 1466 (m), 1235 (s); Anal. calcd. for $C_{13}H_{11}OF$: C, 77.2; H, 5.5. Found: C, 77.2; H, 5.7.

Methyl 4-hydroxybiphenyl-3-carboxylate (6ca). The title compound was obtained from **4c** (133 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 94–95 °C.[47] Yield: 80 mg, 70%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.79 (s, 1H), 8.08 (d, J = 2.4, 1H), 7.71 (dd, J = 8.6, 2.4, 1H), 7.58–7.53 (2H), 7.48–7.40 (2H), 7.34 (m, 1H), 7.07 (d, J = 8.6, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (0), 161.0 (0), 139.9 (0), 134.4 (1), 132.4 (0), 128.8 (1), 128.1 (1), 127.0 (1), 126.6 (1), 118.0 (1), 112.5 (0), 52.3 (3); IR (neat) ν 3170 (w), 2954(w), 1676 (s), 1440 (m), 1345 (m), 1209 (s); MS (EI): m/z 228 ([M]$^+$, 38), 196 (100), 168 (20); HRMS (EI): calcd. for $C_{14}H_{12}O_3[M]^+$: 228.0781, found: 228.0792; Anal. calcd. for $C_{14}H_{12}O_3$: C, 73.7; H, 5.3. Found: C, 73.4; H, 5.0.

Methyl 4′-fluoro-4-hydroxybiphenyl-3-carboxylate (6cb). The title compound was obtained from **4c** (133 mg, 0.5 mmol) and **5b** (101 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 50–52 °C.[1] Yield: 100 mg, 82%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.77 (s, 1H), 8.00 (d, J = 2.4, 1H), 7.63 (dd, J = 8.6, 2.4, 1H), 7.49 (d, J = 8.8, 1H); 7.47 (d, J = 8.8, 1H), 7.12 (d, J = 8.7, 1H), 7.09 (d, J = 8.7, 1H), 7.05 (d, J = 8.7, 1H), 3.98 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (0), 162.3 (d, J = 246.2, 0), 136.0 (d, J = 3.2, 0), 134.2 (1),131.5 (0), 128.1 (d, J = 8.0, 1), 128.0 (1),118.1 (1), 115.6 (d, J = 21.5, 1), 112.5 (0), 52.3 (3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −117.1 (tt, J = 5.3, 3.3); IR (neat): ν 2957 (w), 1679 (m), 1483 (m), 1208 (s); Anal. calcd. for $C_{14}H_{11}O_3F$: C, 68.3; H, 4.5. Found: C, 68.2; H, 4.6.

Methyl 5-(benzo[*d*][1,3]dioxol-5-yl)-2-hydroxybenzoate (6cc). The title compound was obtained from **4c** (133 mg, 0.5 mmol) and **5c** (114 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 134–136 °C. Yield: 60 mg, 44%. ^{1}H NMR (300 MHz,

$CDCl_3$) δ 10.73 (s, 1H), 7.98 (d, J = 2.4, 1H), 7.61 (dd, J = 8.7, 2.4, 1H), 7.06–6.96 (3H), 6.86 (dd, J = 7.8, 0.6, 1H), 5.99 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.5 (0), 160.7 (0), 148.2 (0), 146.9 (0), 134.3 (0), 134.2 (1), 132.2 (0), 127.8 (1), 120.1 (1), 118.0 (1), 112.4 (0), 108.6 (1), 107.2 (1), 101.2 (2), 52.3 (3); IR (neat) ν 3194 (w), 2895 (w), 1628 (m), 1677 (s), 1476 (s), 1223 (s); MS (EI) m/z 272 ([M]$^+$, 64), 240 (100), 126 (86); HRMS (EI) calcd. for $C_{15}H_{12}O_5$[M]$^+$: 272.0679; found: 272.0679; Anal. calcd. for $C_{15}H_{12}O_5$: C, 66.2; H, 4.4. Found: C, 65.9; H, 4.2.

Methyl 4′,6′-difluoro-4-hydroxybiphenyl-3-carboxylate (diflunisal methyl ester, 6cd). The title compound was obtained from **4c** (133 mg, 0.5 mmol) and **5d** (110 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 97–99 °C.[48] Yield: 130 mg, 99%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.83 (s, 1H), 7.97 (dd, J = 2.1, 1.3, 1H), 7.62–7.55 (m, 1H), 7.34 (dd, J = 8.7, 6.4, 1H), 7.05 (d, J = 8.7, 1H), 6.91 (d, J = 8.2, 1H), 6.91–6.84 (m, 1H), 3.96 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3 (0), 162.2 (dd, J = 249.0, 11.9, 0), 161.2 (0), 159.8 (dd, J = 250.1, 11.9, 0), 136.1 (d, J = 3.1, 1), 131.0 (dd, J = 9.4, 4.8, 1), 130.1 (d, J = 6.9, 1), 126.0 (d, J = 1.1, 0), 124.1 (dd, J = 13.6, 3.8, 0), 117.8 (1), 112.4 (0), 111.5 (dd, J = 21.1, 3.8, 1), 104.3 (dd, J = 16.5 15.4, 1), 52.34 (3); ^{19}F NMR (282 MHz, $CDCl_3$) δ −112.6 (m), −115.0 (m); IR (neat) ν 3135 (w), 1678 (s), 1484 (s), 1441 (m), 1212 (m); MS (EI): m/z 264 ([M]$^+$, 45), 232 (100); HRMS (EI) calcd. for $C_{14}H_{10}F_2O_3$[M]$^+$: 264.0598; found: 264.0574; Anal. calcd. for $C_{14}H_{10}F_2O_3$: C, 63.6; H, 3.8. Found: C, 63.6; H, 3.7.

Methyl 4-hydroxy-4′-(morpholine-4-carbonyl)biphenyl-3-carboxylate (6ce). The title compound was obtained from **4c** (133 mg, 0.5 mmol) and **5e** (149 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 120–122 °C. Yield: 120 mg, 70%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.03 (d, J = 2.4, 1H), 7.73 (dd, J = 8.7, 2.4, 1H), 7.60 (d, J = 8.3, 2H), 7.47 (d, J = 8.3, 2H), 6.99 (d, J = 8.7, 1H), 3.94 (s, 3H), 3.40–3.80 (broad due to hindered rotation around the amide bond, 8H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 172.3 (0), 171.6 (0), 162.6 (0), 142.9 (0), 135.4 (1), 135.1 (0), 132.6 (0), 129.3 (1), 129.1 (1), 127.7 (1), 119.3 (1), 114.1 (0), 67.9 (2), 53.2 (3), signal for CH_2N not observed due to hindered rotation and/or quadrupole broadening; IR (neat) ν 2957 (w), 2855 (w), 1676 (s), 1628 (s), 1429 (s), 1340 (m), 1275 (s), 1247 (s), 1209 (s); MS (EI) m/z 341 ([M]$^+$, 51), 255 (95), 223 (100), 139 (65); HRMS (EI) calcd. for $C_{19}H_{19}NO_5$[M]$^+$: 341.1258; found: 341.1278; Anal. calcd. for $C_{19}H_{19}NO_5$: C, 66.9; H, 5.6; N, 4.1. Found: C, 66.7; H, 5.4; N, 4.3.

4-Hydroxybiphenyl-3-carboxylic acid (6da). The title compound was obtained from **4d** (126 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 212–214 °C.[49] Yield: 63 mg, 59%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.07 (d, J = 2.4, 1H), 7.71 (dd, J = 8.6, 2.4, 1H), 7.57–7.50 (2H), 7.43–7.36 (2H), 7.28 (m, 1H), 6.99 (d, J = 8.6, 1H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 173.55, 162.72, 141.38, 135.29, 133.72, 130.03, 129.65, 128.15, 127.60, 118.86, 114.24; IR (neat) ν 2922 (w), 1667 (m), 1447 (m), 1237 (m); MS (ESI) m/z 215 ([M+H]$^+$, 42), 197 (100); HRMS (ESI) calcd. for $C_{13}H_{11}O_3$[M+H]$^+$: 215.0708, found: 215.0716; Anal. calcd. for $C_{13}H_{10}O_3$: C, 72.9; H, 4.7. Found: C, 72.7; H, 4.6.

4′-Fluoro-4-hydroxybiphenyl-3-carboxylic acid (6db). The title compound was obtained from **4d** (126 mg, 0.5 mmol) and **5b** (101 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 204–205 °C.[50] Yield: 40 mg, 34%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.02 (s, 1H), 7.66 (d, J = 8.4, 1H), 7.55–7.45 (2H), 7.17–7.07 (2H), 6.98 (d, J = 8.5, 1H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 173.4 (0), 163.8 (d, J = 244.7, 0), 162.7 (0), 137.7 (d, J = 3.1, 0), 135.2 (1), 132.7 (0), 129.6 (1), 129.4 (d, J = 8.1, 1), 118.9 (1), 116.6 (d, J = 21.7, 1), 114.3 (0); ^{19}F NMR (282 MHz, MeOD-d_4) δ −116.0 (m); IR (neat): ν 2925 (w), 1676 (w), 1516 (w), 1585 (w), 1439 (w), 1200 (m); MS (ESI): m/z 233 ([M+H]$^+$, 35), 215 (100); HRMS (ESI) calcd. for $C_{13}H_{10}FO_3$[M+H]$^+$: 233.0614; found: 233.0597; Anal. calcd. for $C_{13}H_9FO_3$: C, 67.2; H, 3.9. Found: C, 67.1; H, 4.0.

5-(Benzo[*d*][1,3]dioxol-5-yl)-2-hydroxybenzoic acid (6dc). The title compound was obtained from **4d** (126 mg, 0.5 mmol) and **5c** (114 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 241–245 °C. Yield: 59 mg, 46%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 8.00 (d, J = 2.4, 1H), 7.67 (dd, J = 8.6, 2.5, 1H), 7.05–7.03 (2H), 6.98 (d, J = 8.6, 1H), 6.87 (d, J = 8.5, 1H), 5.97 (s, 2H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 173.6 (0), 162.5 (0), 149.9 (0), 148.5 (0), 135.9 (0), 135.2 (1), 133.6 (0), 129.4 (1), 121.2 (1), 118.8 (0), 114.2 (0), 109.7 (1), 108.1 (1), 102.7 (1); IR (neat) ν 2917 (w), 2850 (w), 1665 (m), 1455 (m), 1251 (m); MS (EI): m/z 258 ([M]$^+$, 43), 240 (100), 126 (73); HRMS (EI): calcd. for $C_{14}H_{10}O_5$[M]$^+$: 258.0523; found: 258.0536; Anal. calcd. for $C_{14}H_{10}O_5$: C, 65.1; H, 3.9. Found: C, 65.1; H, 3.8.

4′,6′-Difluoro-4-hydroxybiphenyl-3-carboxylic acid (diflunisal, 1). The title compound was obtained from **4d** (126 mg, 0.5 mmol) and **5d** (110 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 204–206 °C.[51] Yield: 42 mg, 34%. ^{1}H NMR (300 MHz, MeOD-d_4) δ 7.97 (s, 1H), 7.60 (dd, J = 1.5, 8.6, 1H), 7.43 (dd, J = 7.9, 15.6, 1H), 7.05–6.95 (3H); ^{13}C NMR (75 MHz, MeOD-d_4) δ 173.4, 163.7 (dd, J = 247.5, 11.9), 163.0, 161.2 (dd, J = 248.7, 11.9) 137.1 (d, J = 2.9), 132.6 (dd, J = 9.5, 4.8), 131.9 (d, J = 3.1), 127.2, 125.7 (dd, J = 13.6, 3.9), 118.6, 114.2, 112.8 (dd, J = 21.4, 3.8), 105.3 (dd, J = 27.1, 25.8); ^{19}F NMR (282 MHz, MeOD-d_4) δ −111.3 (m), −113.3 ("q", J = 9.9); IR (neat): ν 3344 (s), 2950 (w), 2838 (w), 1651 (m), 1450 (m); MS (EI) m/z 250 ([M]$^+$, 50), 232 (100); HRMS (EI) calcd. for $C_{13}H_8F_2O_3$[M]$^+$: 250.0442. Found: 250.0449; Anal. calcd. for $C_{13}H_8F_2O_3$: C, 62.4; H, 3.2. Found: C, 62.5; H, 3.6.

3-Nitrobiphenyl-4-ol (6ea). The title compound was obtained from **4e** (127 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 65–67 °C.[52] Yield: 100 mg, 94%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.59 (s, 1H), 8.33 (d, J = 2.1, 1H), 7.84 (dd, J = 8.7, 2.2, 1H), 7.50–7.44 (2H), 7.46–7.39 (2H), 7.39 (m, 1H), 7.25 (d, J = 8.7, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3 (0), 138.2 (0), 136.3 (1), 133.9 (0), 133.8 (0), 129.1 (1), 128.0 (1), 126.7 (1), 122.8 (1), 120.4 (1); IR (neat) ν 3243 (w), 3032 (w), 1628 (m), 1536 (s), 1476 (s), 1310 (s); MS (EI) m/z 215 ([M]$^+$, 13), 181 (100), 130 (28); HRMS (EI): calcd. for $C_{12}H_9NO_3$[M]$^+$: 215.0582; found: 215.0596; Anal. calcd. for $C_{12}H_9NO_3$: C, 67.0; H, 4.2; N, 6.5. Found: C, 67.0; H, 4.2; N, 6.4.

3-Bromobiphenyl-4-ol (6fa). The title compound was obtained from **4f** (143 mg, 0.5 mmol) and **5a** (92 mg, 0.5 mmol) using base-free conditions as a colourless solid, mp 94–95 °C.[53] Yield: 55 mg, 44%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, J = 2.2, 1H), 7.54–7.49 (2H), 7.48–7.39 (3H), 7.33 (m, 1H), 7.09 (d, J = 8.4, 1H), 5.54 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.6 (0), 139.4 (0),

135.4 (0), 130.4 (1), 128.8 (1), 127.9 (1), 127.2 (1), 126.7 (1), 116.3 (1), 110.6 (0); IR (neat) ν 3320 (m), 2360 (w), 1488 (m) 1450 (m) 1412 (s) 1273 (s); MS (EI) m/z 248 ([M]$^+$, 100), 139 (80), 115 (25); HRMS (EI) calcd. for $C_{12}H_9BrO$[M]$^+$: 247.9831; found: 247.9836; Anal. calcd. for $C_{12}H_9BrO$: C, 57.9; H, 3.6. Found: C, 57.6; H, 3.5.

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